

REMARKS

Amendments

Claim 1 is currently amended. Claim 8 is cancelled. Claims 1, 3, 4, 6-7, and 9-13 remain in the Application.

Claim 1 has been amended such that the torsemide-forming reaction is conducted in the absence of water. Claim 1 has also been amended such that the torsemide-forming reaction is conducted in the presence of an organic solvent selected from the group consisting of ethyl acetate, acetonitrile, acetone, methyl isobutyl ketone and mixtures thereof. The Applicant respectfully submits that the amendments do not constitute new matter. Support for the amendments to Claim 1 can be found in the disclosure on page 2, paragraph 31 and the examples.

Obviousness

The Examiner has rejected Claims 1, 3, 4, 6-13 as being obvious in light of Gutman *et al* (WO 03/097603) and in view of Wouters *et al* (Eur. J. Med. Chem. vol. 35 pp 923-929). Applicant has amended Claim 1 in order to advance the prosecution and traverse the Examiner's rejection. Therefore, reconsideration of Claims 1, 3, 4, 6-7, and 9-13 are respectfully requested.

The Examiner is of the position that on page 14 (steps f to h) Gutman *et al* teaches the reaction of 4-*m*-tolylamino-3-pyridinesulfonamide, lithium (bi)carbonate and isopropylcarbamate in water. In contrast, Applicants process is performed in one of four organic solvents and in the absence of water. By doing so, Applicant's process achieves excellent reaction yield and product purity. Furthermore, performing the reaction in a strictly organic solvent, *i.e.* not in a mixture with water, allows for the precipitation of resulting torsemide salt product upon cooling of the reaction mixture (*e.g.* page 2, paragraph 23 of application). The precipitation event allows for the isolation of highly pure torsemide salt by simple filtration. Such ease of purification is highly practical and advantageous for process scale applications.

The Examiner states that Wouters *et al* teach the analogous process using an 'organic solvent', purported to be a 50:50 mixture of acetone and water. Applicants maintain that the Wouters *et al* article does not include any experimental details documenting a synthesis of torsemide in that solvent system. Rather, as stated in the final sentence of page 927, "[t]he synthesis of compounds 1 [torsemide] ... has been described previously" in the literature (*i.e.* Delarge J., Ann. Pharm. Fr. 36 (1978) 369-380). The clear implication being that Wouters *et al* synthesized torsemide by repeating the teachings of Delarge. In fact, Wouters *et al* do not include any experimental details to support the use of a 50:50 acetone:water solvent mixture. Even if Wouters *et al* did perform the reaction in a 50:50 acetone:water mixture, the formation of torsemide is not conducted in the absence of water, as in claim 1.

Respectfully, the Applicants maintain that the use of water as a solvent for a reaction using isopropylisocyanate cannot lead to a favorable reaction. As discussed in the Applicant's December 8, 2006 response, isopropylisocyanate reacts in a deleterious manner in the presence of water to give undesirable urea by-products (see Shkapenko *et al* Ind. Engineer. Chem. 1960 vol52 pp605-608 (enclosed)). Furthermore, the use of water as a solvent inhibits the precipitation of torsemide salts at the conclusion of the reaction, due to their high solubility in water. Consequently, the necessary purification in the Wouters *et al* process is considerably more cumbersome and not amenable to process scale preparation of torsemide.

The Applicants maintain that the combination of the teachings of Gutman *et al* and Wouters *et al* results in an inferior process with respect to yield, purity, ease of operation, and amenability to a process scale. Furthermore, even if the combination of the Gutman and Wouters reference was favorable, there exists no motivation or suggestion in either reference, or the broader art, to do so.

Notably, in the recent Supreme Court decision *KSR v. Teleflex*, the Court recognized that the demonstration of teaching, suggestion, or motivation to combination prior art to meet the claimed subject matter could provide insight in ascertaining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). Respectfully, Applicants fail to see how the Examiner has established a reason why a person of ordinary skill in the art would have combined the prior art elements without relying on significant hindsight.

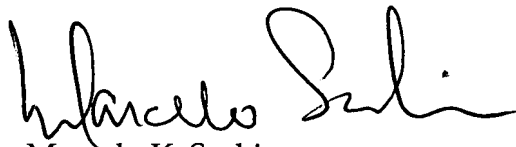
The Examiner's arguments have no bearing on the patentability of Claims 3 and 4, which cover a distinct reaction step. Claims 3 and 4 are specific to processes for the formation of compound II, which are not disclosed by either Gutman *et al* or Wouters *et al*. Respectfully, reconsideration of Claims 3 and 4 is requested.

In view of the above submissions, Applicant respectfully submits that claims 1, 3, 4, 6-7, and 9-13 are not rendered obvious by the teachings of Gutman *et al* and Wouters *et al*. Applicant respectfully requests reconsideration by the Examiner of claims 1, 3, 4, 6-7, and 9-13.

In view of the above, the Applicant submits that claims 1, 3, 4, 6-7, and 9-13 are unobvious and patentable over Gutman *et al* WO 03/097603 in light of Wouters *et al* under USC 103. Therefore, Applicant respectfully submits that the above-identified application is allowable.

If the Examiner has any questions, he is respectfully requested to contact Applicant's Agent, Marcelo K. Sarkis at (905) 771-6414 collect at the Examiner's convenience.

Respectfully submitted,
IVOR M. HUGHES

A handwritten signature in black ink, appearing to read 'Marcelo Sarkis', with a stylized, cursive script.

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Enclosures:

- 1) Petition for Extension of Time Under 37 CFR 1.136(a) (Form PTO/SB/22)
- 2) Cheque \$120.00 U.S.
- 3) Shkapenko *et al* Ind. Engin. Chem. 1960 vol52 pp605-608